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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/574,460	05/18/00	APICELLA M	875.009US1

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HM12/0507

EXAMINER	
PAK, Y	
ART UNIT	**PAPER NUMBER**
1652	8

DATE MAILED: 05/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/574,460	APICELLA ET AL.	
	Examiner	Art Unit	
	Yong Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 5-9, 11-12, 14, and 16-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-9, 11-12, 14, and 16-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

The amendment filed on November March 29, 2001 (in Paper No. 7), canceling claims 2-4, 10, 13 and 15 has been entered.

Claims 1, 5-9, 11-12, 14, and 16-17 are pending.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1, 5-9, 11-12, 14 and 16-17) in Paper No. 7 is acknowledged.

Drawings

Drawings filed concurrently with the application has been objected by the Draftsman. Please refer to the attached PTO-948 form for details.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-9, 11-12, 14, and 16-17are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 11, and 16 are drawn to a process of producing oligosaccharides in bacteria expressing an enzyme capable of adding acceptor molecules and a glycosyltransferase from any source. These claims comprise a vast diverse genus of microorganisms wherein the lipooligosaccharide have different lipid core structures, thereby requiring enzymes with different substrate specificity corresponding to different lipid core structures. The specification only describes producing oligosaccharides, as represented in Figure 3, in Escherichia coli K-12 transformed with *rfe*, a UDP-GlcNAc: Undecaprenol GlcNAc-1 phosphate transferase of *Haemophilus influenzae* and a lipooligosaccharide-synthesis gene (*lsg*) from *H. influenzae*. It is unpredictable if rfe will add acceptor molecules to the heptose of the lipid core structure in all bacteria and if the lsg or other glycosyltransferases will add monosaccharides to the core in all bacteria. Therefore, the specification describes one representative species of a diverse genus and fails to teach common identifying characteristics that would allow predicting bacteria as a proper production cell for using the two glycosyltransferases and *rfe*.

Secondly, the claims encompass any glycosyltransferase and any enzymes capable of adding an acceptor molecule to heptose. The specification describes other glycosyltransferases having different functions, such as being a galactosyltransferase. However, it is unpredictable if glycosyltransferase and enzyme capable of adding acceptor molecules from any source will function correctly in *E. coli* K-12. Therefore, the specification fails to describe the common identifying characteristics that would allow predicting a glycosyltransferase or enzymes adding acceptor molecules as being able to function in *E. coli* K-12 cells.

Lastly, these claims encompass a method of producing a genus of oligosaccharide structures using a genus of glycosyltransferase. The specification does not describe oligosaccharide structures of lipooligosaccharides belonging to organisms other than *H. influenzae*. Therefore, the specification does not describe all enzymes necessary of adding specific monosaccharides and acceptor molecules to produce any oligosaccharides in the whole genus. Also, the specification fails to describe enzymes by structural properties and identifying characteristics other than the generic functionality of transferring monosaccharides and acceptor molecules.

Given this lack of the description of the representative species encompassed by the genus of the claims used in the method of sialylating glycoproteins, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 1, 5-9, 11-12, 14, and 16-17.

Claim 1, 5-9, 11-12, 14, and 16-17are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing lipooligosaccharides as shown in Figure 3 and lipooligosaccharides in *E. coli* K-12 cells transformed with lsg and rfe, does not reasonably provide enablement for producing oligosaccharides having different structures as shown in Figure 3 in bacteria other than *E. coli K-12* expressing enzymes other than lsg and rfe. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification gives inadequate guidance in producing oligosaccharides having any structures in any bacterial cells expressing glycosyltransferase and an enzyme, from any source, adding any monosaccharides and acceptor molecules to the heptose molecule of the lipid core structure, respectively. Applicants teach production of oligosaccharides, as represented in Figure 3, with *E. coli* K-12 cells expressing lsg and rfe. Applicants fail to give guidance on which bacterial cells are a proper host for use of the glycosyltransferases and rfe because it is unpredictable if the glycosyltransferases and rfe can correctly function in bacterial cells having a lipid core structure different from *E. coli* K-12. Also, applicants do not teach which glycosyltransferases and enzymes capable of adding acceptor molecules can be used in E. coli K-12. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

Further, these claims encompass a method of producing oligosaccharide of any structures. Specific glycosyltransferases and enzymes are required to transfer specific monosaccharides and acceptor molecules in elongating the lipid core structure. However, the specification does not teach which glycosyltransferases and which

enzymes capable of adding acceptor molecules to use in producing oligosaccharide structure different from the structures shown in Figure 3.

Therefore, one of ordinary skill would require guidance to produce oligosaccharides with structures different from Figure 3 and to produce oligosaccharides using glycosyltransferase and enzyme capable of adding acceptor molecules different from lsg and rfe, respectively, in non *E. coli* K-12 bacterial cells. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-9, 11-12, 14 and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 5-9, 11-12, 14 and 16-17, the method steps are indefinite and confusing. The claims do not clearly state whether the core lipid structure and the enzyme catalyzing the addition of the acceptor molecule are inherently present in the production cell, which is then transformed by inserting a DNA encoding a glycosyltransferase that synthesizes LPO, LPS or complex carbohydrates. A more clearly defined method steps will overcome this rejection.

In claims 1, 8-9, 11 and 16, the term "glycotransferase" is unclear. It appears that applicants have intended "glycosyltransferase" instead because enzymes that

transfer a saccharide from one molecule to another are referred to as glycosyltransferase.

In claims 8-9, enzymes are presumed to be functional and in other claims, the term "functional" is not used in conjunction with an enzyme. Therefore, the term "functional" is redundant and applicants may wish to delete this term.

In claims 12 and 14, it is unclear if the isolated DNA sequence is encoding a glycosyltransferase or other enzymes.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4-8 11, 12

Claims 1, 5-8, 11-12 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Kwaik et al.

Kwaik et al. (form PTO-1449) teach a method for producing complex carbohydrates and oligosaccharides by transforming *E. coli* K-12 strain JM 109 with vectors comprising *H. influenzae* type b (Hib) LOS biosynthesis gene that is identical to the vector in the instant application (page 2478, 2nd column through page 2479, 1st column and in the specification, page 10, line 22 through page 11, line 19). Art and the specification teach that E. coli K-12 has a terminal heptose molecule in the inner core and acceptor molecules (page 4, lines 24-25). Kwaik et al. teach that the cloned Hib

genes are responsible for assembly of three oligosaccharide components on E. coli LPS and that the glycosyltransferase genes are present in at least three loci within in the Hib fragment (page 2477 2nd column). Glycosyltransferase by definition adds monosaccharides, such as glucose or galactose, from one molecule to another. Therefore, the teachings of Kwaik et al. anticipate claims 1, 5-8, 11-12 and 16-17.

Claims 1, 5, 7, 9, 11, 14 and 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Gotschlich et al.

Gotschlich et al. (form PTO-1449 U.S. Patent No. 5,705,367) teach a method of producing complex carbohydrates and oligosaccharides by introducing a DNA molecule encoding a *Neisseria gonorrhoeae* glycosyltransferase to *Escherichia coli* (Column 14, line 35 through Column 18 line 48). Art and the specification teach that E. coli K-12 has a terminal heptose molecule in the inner core and acceptor molecules (page 4, lines 24-25). Further, Glycosyltransferases by definition add monosaccharides, such as glucose or galactose, from one molecule to another. Therefore, the teachings of Gotschlich et al. anticipate claims 1, 5, 7, 9, 11, 14 and 16-17.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 703-308-9363. The examiner can normally be reached on Monday through Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The

fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Yong Pak
Patent Examiner

May 4, 2001

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